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PRINCIPAL INVESTIGATOR: Eugene D. Kwon, M.D., Ph.D.

CONTRACTING ORGANIZATION: Mayo Clinic Rochester
Rochester, MN 55905

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Eugene D. Kwon, M.D., Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Mayo Clinic Rochester
Rochester, MN 55905

E-Mail: kwon.eugene@mayo.edu

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The induction of tumor-specific T cells remains a primary obstacle to immunotherapeutic approaches for most cancers including prostate cancer. This difficulty has been largely ascribed to mechanisms for tumor evasion of the immune system and host-imposed restrictions (collectively referred to as tolerance) that prevent cross-reactive autoimmunity against the parent tissues from which tumors arise. Limitations in techniques to identify novel and truly immunogenic prostate-specific antigens and efficient methods to modify autologous tissues for vaccine preparation have further constrained approaches to develop immune-based therapies for prostate cancer. Hence, relatively straightforward manipulations that induce specific T cell responses against prostate tumors or epithelial tissues, especially in vivo, might ultimately prove valuable for prostate cancer immunotherapy. This study explores combined androgen ablation (AA) + CTLA-4 blockade immunotherapy as a means of potentiating T cell-mediated responses against prostate tumors to improve overall treatment of advanced prostate cancer.

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INTRODUCTION.

Although androgen ablation (AA) has long served as a mainstay of treatment for patients with advanced prostate cancer, this form of therapy is only palliative. Consequently, nearly all of the ~35,000 men who will die of prostate cancer each year will do so after failing AA therapy. For patients with advanced prostate cancer, median duration of treatment response averages ~2 years following institution of AA therapy. Upon failure of AA therapy, when metastatic hormone-refractory prostate cancer progression becomes apparent, median survival averages only another 16-20 months. While a number of investigational agents have demonstrated some promise for patients who have failed AA, to date, no agent or combined regimen has been shown to confer a survival advantage in randomized clinical testing. Thus, novel approaches for treating advanced prostate cancer – particularly interventions capable of acting synergistically with AA therapy -- are needed. This clinical phase II trial will test whether a specific form of immunotherapy, CTLA-4 blockade, can be used to enhance treatment responses in patients with advanced prostate cancer being treated with AA therapy. CTLA-4 is a T-cell receptor that mediates downregulation of T-cell function. CTLA-4 blockade refers to the administration of a monoclonal antibody (MDX- CTLA-4) that binds the T-cell CTLA-4 receptor to prevent inhibition of T-cell function.

It has been established that CTLA-4 blockade immunotherapy is capable of potentiating host T cell-mediated responses against a number of tumors including prostate cancer, and that the antitumoral capability of CTLA-4 blockade can be markedly enhanced by combining CTLA-4 blockade with manipulations that induce tumor/tissue-specific T cells. Finally, it has recently been shown that androgen ablative (AA) therapy promotes prostate tissue infiltration by T cells that may exhibit specific activity against prostate epithelial/tumor cells. It is, therefore, hypothesized that AA therapy can be used to coax prostate tissues to behave as "in situ vaccines" to induce prostate tissue/tumor-specific T cells (refer to schematic; right). Such prostate-specific T cells induced by AA therapy might then be amenable to immunotherapeutic potentiation by CTLA-4 blockade. If so, T cell responses raised by AA therapy and then bolstered by CTLA-4 blockade would be expected to contribute to tumor rejection, ultimately manifesting in improved treatment outcome for patients with advanced prostate cancer.

In contrast, T cell responses in patients treated with AA therapy alone would be expected to wane, ultimately giving way to tumor progression. Hence, to test whether combined AA therapy plus CTLA-4 blockade is capable of eliciting clinical treatment responses superior to those provided by standard AA therapy alone, and to further test that such treatment advantages emanate from potentiation of host T cell-mediated antitumoral immunity by CTLA-4 blockade, the following prospective randomized clinical phase II trial is proposed.

The primary endpoint for this study is proportion of patients remaining free of disease progression. The time to disease progression (progression-free interval), is defined as the interval from the start of AA therapy until PSA progression. Secondary endpoints will include assessments of initial PSA response to treatment. Tertiary endpoints will include exploratory correlative assessments of prostate-specific as well as generalized host T cell response to treatment. For the cross over component of this trial in which control group subjects will receive CTLA-4 blockade upon progression, the cross over study endpoint will be an alternate definition of PSA response (regression, stabilization or progression). The immunologic studies proposed in this protocol may prove relevant to recent observations suggesting that clinical responses to AA therapy are, at least in part, predicated upon an immune response by the host. If true, immunologic endpoints in this study might ultimately be applicable for identifying patients at greatest risk of failing AA therapy, and who might benefit from early and aggressive intervention.

BODY.

We are currently prepared to open accrual onto our phase II trial entitled "*A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy and CTLA-4 Blockade as a Treatment for Advanced Prostate Cancer*" here at Mayo. It is also anticipated that accrual onto this study will open shortly at UCSF (E. Small, PI) which represents the sister site for this protocol. Until now, our efforts have largely been dedicated towards final development of our phase II protocol, as well as acquistion of requisite approval from the respective IRB's at Mayo, UCSF and the DOD. Additionally, we have requested and secured an IND from the FDA that authorizes our study of combined MDX-CTLA-4 and AA therapy for treatment of advanced prostate cancer. The key steps that we have dealt with in order to open this study are outline in what follows below.

- 01/18/01 Concept approved by the Cancer Center Support Grant Concept Review Committee
- 07/31/02 Submitted for review by the Mayo Cancer Center Protocol Review Committee
- 08/07/02 Approved by the Mayo Cancer Center Protocol Review Committee with minor modifications and pending sign-off by Dr. J. O'Fallon
- 08/23/02 Protocol submitted for IRB approval
- 08/23/02 IRB deferred; further consideration will require 13 items (see minute/file)
- 08/25/02 Dr. Kwon application for IND (cross-referencing Medarex BB-IND 8937).
- 08/29/02 IRB approval received; correspondence involved 10 items; CF approved with revisions
- 09/10/02 Assignment of IND BB-IND 10,655 to Dr. Kwon.
- 10/03/02 Communication with FDA (Dr. Lee Pai Scherf, Medical reviewer for IND) to clarify protocol.
- 10/05/02 Clarification of protocol and changes submitted to FDA (Dr. Pai Scherf).

- 10/31/02 IRB approved Investigator Brochure (Edition 3.0); no CF revisions were made
- 11/07/02 Andrea Kline requested additional information prior to scheduling for review by the Human Subjects Research Review Board (HSRRB). Issue pertaining to coverage of research-related injury raised by Mayo and DOD.
- 03/06/03 IRB approved consent form changes to comply with HIPAA
- 04/17/03 Revised clinical protocol, revised consent, and responses to the DOD IRB sent to Andrea Kline
- 05/05/03 Andrea Kline requested additional information prior to Human Subjects Research Review Board (HSRRB) meeting scheduled for 05/14/03
- 05/05/03 Dr. Kwon provided additional information to Andrea Kline
- 05/09/03 Andrea Kline forwarded two questions from an MSRRB member's pre-review of the protocol
- 05/12/03 Dr. Kwon responded to Andrea Kline and provided a response to the DOD IRB pre-review questions
- 05/14/03 Dr. Kwon teleconference with the DOD HSRRB (IRB) board for review and approval of protocol.
- 05/15/03 Further clarifications of the protocol submitted to DOD HSRRB in response to teleconference of 15/14/03.
- 06/12/03 HSRRB approved revised protocol
- 07/03/03 Andrea Kline informed Dr. Kwon, via e-mail, to "submit these revised versions to the Mayo Clinic IRB for its review and approval of the changes the HSRRB requested. Once we (the HSRRB) have received documentation of the IRB's approval and a copy of the IRB-stamped consent form, the project can receive final approval from our (the HSRRB) office."
- 07/21/03 Progress report received by the IRB
- 08/14/03 IRB approval received for progress report
- 08/14/03 IRB approval received for modification request dated 8/4/03 (see minute/file)
- 08/26/03 BB-IND 10,655: Annual Report of Progress (Serial Number 002) submitted (Form FDA 1571).
- 09/02/03 Dr. Kwon informed Andrea Kline that the Mayo IRB approved the modification
- 09/19/03 Dr. Kwon forwarded the Mayo IRB approval minute and consent to Andrea Kline
- 09/25/03 Andrea Kline questioned missing HSRRB-recommended changes to the consent
- 09/25/03 Dr. Kwon responded that some of the HSRRB-recommended changes to the consent were unacceptable to the Mayo IRB
- 09/30/03 Mr. Tibor Tuzson asked if an older version of the consent was approved by the Mayo IRB; there were discrepancies
- 10/09/03 Modification received by the IRB
- 10/30/03 IRB approval received for modification dated 10/6/03; involves revisions to the CF
- 11/11/03 IRB approval minutes forwarded to Andrea Kline
- 11/18/03 Dr. Kwon received an e-mail from Andrea Kline stating that an approval memo for the protocol was sent to the USAMRAA Contracting Office and

that this office would contact the Mayo Clinic grant office regarding permission to implement this protocol in the near future.

- 02/13/04 Sharri Hackbarth, Mayo Research Administrator, received letter from USAMRAA with "copies of Modification No. P00001 for Grant No DAMD17-02-1-0245 fully executed for your information and file."

KEY RESEARCH ACCOMPLISHMENTS.

- Protocol written and fully approved by the Mayo IRB and DOD HSRRB.
- Resolved issues pertaining to patient coverage for research-related injury.
- Secured IND BB 10,655 from FDA.
- Protocol in final stage of approval by UCSF IRB.

REPORTABLE OUTCOMES TO DATE.

None

CONCLUSIONS.

In summary, we have now accomplished the necessary steps to open our phase II trial entitled "*A Phase II Immunotherapeutic Trial: Combination Androgen Ablative Therapy and CTLA-4 Blockade as a Treatment for Advanced Prostate Cancer*" here at Mayo. Accrual onto this study will also open at UCSF very shortly. It is our sincere hope that this trial will ultimately demonstrate that T cell-mediated responses against prostate tumors, induced by an inductive period of androgen ablation, will be immunotherapeutically potentiated by anti-CTLA-4 mAb therapy to improve overall treatment for patients that initially present with advanced prostate cancer.

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